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20. (Twice Amended) A pharmaceutical composition according to claim 19 wherein
said fusion protein comprises a polypeptide according to claim [2] 4.

Add the following claim.

Ch G8 -26. An isolated fusion protein comprising (1) a sequence of amino acids corresponding
to a fragment or a derivative of a heavy chain of a type F botulinum neurotoxin, which is (a) free
of botulinum toxin activity, (b) is free of toxoid, and (c) elicits, in a mammal, an immunological
response that is protective against type F botulinum toxin, and (2) a polypeptide that facilitates or
enhances purification of the fusion protein.--

REMARKS

Reconsideration is requested.

Claims 1 and 2 have been canceled, without prejudice. Claims 3-26 are pending. Claims
3-12, 19-24 and 26, are active. Claims 13-18 and 25 have been withdrawn. The applicants have
not received a decision on their Alternate Petition and request the same as the Examiner
indicated would be forthcoming at page 2 of the Office Action of March 16, 2000 (Paper No.
14). The applicants note the Petition was submitted January 7, 2000, over six months ago, and a
decision is requested without further delay. The Examiner's assistance in urging the
Commissioner to forward his decision to the undersigned would be appreciated.

The Examiner's comment at page 4 of Paper No. 14 that claims 13-18 and 25 have been
withdrawn and a "complete reply to the final rejection must include cancellation of non-elected

claims or other appropriate action" is not understood as the present Office Action does not contain a final rejection and the applicants are unable to act in this regard in light of not having yet received a decision on their Alternate Rule 181 Petition.

Claim 3 has been amended above to include the details of claims 1 and 2, which have been canceled, and also to indicate that the claimed polypeptide contains a fragment or derivative of the recited botulinum neurotoxin and is a polypeptide which must have the characteristics of being free of botulinum toxin activity, free of toxoid and eliciting, in a mammal, an immunological response as protective against type F botulinum toxin. The claimed polypeptide therefore would be understood by one of ordinary skill, in view of the present specification, to require more than a single amino acid.

The Section 101 rejection of claims 7 and 9-10 is obviated by the above amendment to claim 7 which further indicates that the claimed composition includes isolated polypeptides. Withdrawal of the Section 101 rejection of claims 7 and 9-10 is requested.

The Section 112, first paragraph, rejection of claims 7-11 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Initially, the applicants note that claims 8 and 11 have been amended above to no longer be dependent from claim 7 such that the Section 112, first paragraph, rejection of the same, as being dependent on claim 7, is no longer appropriate. Moreover, withdrawal of the rejection with regard to claims 7, 9 and 10 is also requested as, contrary to the Examiner's assertions, the application provides a description at, for example, at page 5, lines 21-24, of an example of compositions of claims 7, 9 and 10. Given this disclosure, one of ordinary skill in the art would have appreciated how to make and use the claimed invention without undue experimentation. The Examiner is urged to appreciate that the art of purification of proteins at the time of the

present invention was advanced and the use of antibodies and antibody fragments, for example, to aid in protein purification was well known and highly advanced. Accordingly, withdrawal of the Section 112, first paragraph, rejection of claims 7-11, is requested.

The Section 112, first paragraph, rejection of claims 22-24 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The applicants respectfully submit that claims 22-24 are enabled by the specification, especially in view of the example of protective immunity against *C. botulinum* provided on pages 13-14 of the present specification. The Examiner cites Jobling (*Molecular Microbiology* (1991) 5(7), 1755-1767) as an alleged example of the unpredictability of mutations as to confirmation, immunological recognition, binding and toxicity. The applicants respectfully note, however, that Jobling, which was published four years before the present priority date actually demonstrates that it would require only a reasonable amount of experimentation to make and use the presently claimed invention. That is, the level of ordinary skill in the art of peptide synthesis, purification and testing was advanced, even as of 1991, such that given the known structure and function of botulinum toxin, as described in the present application, and the ability to test botulinum toxin as of the time of the present invention, combined with the teaching of the present application, it would have required only a reasonable amount of experimentation to make and use the presently claimed invention. As for the Examiner's interpretation of "protection" the applicants respectfully submit that one of ordinary skill in this art would interpret the exemplification of the present specification as demonstrating "protection" by an exemplary embodiment of the presently claimed invention. Withdrawal of the Section 112, first paragraph, rejection of claims 22-24 is requested.

The Examiner's comments in ¶¶ 13 and 14 of Paper No. 14, which do not specifically contain a rejection of any claim, is obviated by the above amendments. As noted above, claims 8 and 11 are no longer dependent on claim 7. Moreover, claims 9 and 10 have been amended for clarity. The Examiner is invited to contact the undersigned if anything further is required in this regard.

The Section 102 rejection of claims 1-2, 12 and 22 over Sesardic (WO 94/21684) is obviated by the above amendments which cancel claims 1 and 2, without prejudice, and amend unrejected claim 3 to include the details of canceled claims 1 and 2. Withdrawal of the Section 102 rejection of claims 1-2, 12 and 22 over Sesardic is requested.

The Section 102 rejection of claims 3-4, 7-10 and 19-24 over Sesardic "as evidenced by Sigma Catalog 1992" is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner's rejection appears to be based on an assertion that a single amino acid residue of Sesardic is sufficient to anticipate the unamended claim 3. As noted above, however, claim 3 has been amended to clearly indicate that the polypeptide of the claim, which includes a fragment or derivative of a heavy chain of a type F botulinum neurotoxin, elicits, in a mammal, an immunological response that is protective against type F botulinum toxin. The Examiner has not indicated where the reference teaches, literally or inherently, such a response by use of the single amino acid residue of the cited reference. Moreover, it is unclear how the addition of the Sigma reference in the rejection of ¶17 of Paper No. 14 aids in the interpretation of Sesardic with regard to claim 3 where Sesardic alone was not deemed sufficient by the Examiner to reject claim 3 in ¶16 of Paper No. 14 over Sesardic alone. The Examiner appears to only rely on the Sigma Catalog reference in ¶17 of Paper No. 14 in reference to claims 8-10. Withdrawal of the

Section 102 rejection of claims 3-4, 7-10 and 19-24 over Sesardic "as evidence by Sigma Catalog 1992" is requested.

The Section 102 rejection of claims 1-4, 7-12 and 19-24 over Simon (U.S. Patent No. 5,178,859) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Simon fails to teach the presently claimed polypeptide which elicits, in a mammal, immunological responses protective against type F botulinum toxin or methods of production or use of the same. Moreover, Simon fails to meet the structural requirements of the presently claimed invention which require a polypeptide comprising a fragment or a derivative of a heavy chain of a type F botulinum neurotoxin. Reconsideration and withdrawal of the Section 102 rejection of claims 1-4, 7-12 and 19-24 over Simon are requested.

In view of the above, the claims, as amended, are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,
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